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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/017,718	12/14/2001	Karl H. Weisgraber	UCAL-222	5282

24353 7590 04/20/2004

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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 04/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

SM -

Office Action Summary	Application No.	Applicant(s)	
	10/017,718	WEISGRABER ET AL.	
	Examiner	Art Unit	
	Thai-An N Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5,7 and 9-22* is/are pending in the application.

4a) Of the above claim(s) *9-13 and 16-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5,7,14,15 and 20-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' Amendment and Response, filed 1/23/04 has been entered.

Claims 20-22 have been added. Claims 1, 3, 5, 7 and 9-22 are pending. Claims 9-13 and 16-19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected groups, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 8. Claims 1, 3, 5, 7, 14, 15, 20-22 are under current examination.

As stated in Applicants' Response, the Examiner will consider claims 5 and 7 with the previously examined claims.

Claim Objections

The prior objection of claim 15 is withdrawn in view of Applicants' amendment.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 5, 7, 14, 15, 20-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The

claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that, "[A]pplicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." *Vas-Cath Inc. v. Mahurkar,* 19USPQ2d at 1117. The specification does not, "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." *Vas-cath Inc. v. Mahurkar*, 19USPQ2d at 1116.

The specification teaches that human apoE4 exhibits domain interaction due to the presence of an Arg-112, together with an Arg-61, and a Glu-255, and that mouse apoE contains the *equivalent* of Arg-112 and Glu-255, but lacks the critical Arg-61 required for domain interaction. Instead, the mouse apoE contains a Thr-61. See p. 3, ¶ 0009. The claimed invention is directed to mice, cells and methods of using the mice wherein a modified endogenous apoE polypeptide comprises a Thr→Arg substitution at a position equivalent to amino acid 61 of human apoE4. The specification fails to provide adequate written description for a Thr→Arg substitution at a position equivalent to amino acid 61 of human apoE4, as claimed, to indicate that Applicants had possession of the claimed invention. The claimed invention as a whole is not adequately described if the claims require essential or

critical elements which are not adequately described in the specification, and which are not conventional in the art as of Applicants' effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics (as it relates to the invention as a whole) such that one of skill in the art would recognize the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). In the instant case, the claimed embodiment of a Thr→Arg substitution at a position equivalent to amino acid 61 of human apoE4 lacks a written description. The specification fails to describe what position(s) in an endogenous mouse apoE4 protein would be considered equivalent to the amino acid 61 of the human apoE4. The skilled artisan could not envision such equivalent positions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolation. See *Fiers v. Revel,* 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGFs were found to be unpatentable due to lack of written description for that broad class. The specification only provided the bovine sequence.

Applicant is reminded that *Vas-Cath* makes clear that the written description of 35 U.S.C. 112 is severable from its enablement provision [see p. 1115].

Claims 1, 3, 5, 7, 14, 15, 20-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention.

The claimed transgenic mice, cells isolated from the mice, and methods of utilizing the mice in methods of identifying agents are not enabled because the specification fails to provide teachings or guidance with regard to the particular human sequence with amino acid 61 which would be used to identify the amino acid equivalent in the mouse sequence. The specification teaches the generation of a non-human gene-targeted animal for the study of apolipoprotein E4 [apoE4] pathologies, wherein the endogenous apoE of the gene targeted animal is genetically altered such that the encoded recombinant apoE polypeptide exhibits domain interaction. It is this domain interaction that is representative of human apoE4 domain, and as such, these animals can be used as models for human apoE4 domain interaction. In particular, the specification teaches a gene-targeted mouse comprising a modified mouse apoE4 gene, wherein the modification comprises a

Thr→Arg substitution at a position equivalent to the amino acid 61 of human apoE4. See p. 6, ¶ 0020.

MPEP §608.01 (p) states that:

> *A disclosure in an application, to be complete, must contain such description and details as to enable any person skilled in the art or science to which the invention pertains to make and use the invention as of its filing date. In re Glass, 492 F.2d 1228, 181 USPQ 31 (CCPA 1974). While the prior art setting may be mentioned in general terms, the essential novelty, the essence of the invention, must be described in such details, including proportions and techniques, where necessary, as to enable those persons skilled in the art to make and utilize the invention.*

The specification is not enabling for the instant invention because it fails to teach the particular sequence that would be used such that one of skill in the art would be able to identify the amino acid substitution equivalent to amino acid 61 in human apoE4. Note that the identification of amino acid number 61 in the human apoE4 would be relative to the sequence used. After careful review of the specification, the Examiner is unable to identify the particular human sequence that would be used (by SEQ ID NO., for example) in the methods as claimed, such that one of skill in the art would be able to identify both amino acid 61 of the human apoE4 and a position equivalent to that amino acid in the mouse apoE4 gene. If Applicants feel that the human apoE4 amino acid sequence is present in the instant specification, Applicants are invited to specifically point to page and line number as to where this sequence can be found. The human amino acid sequence of apoE4 is considered essential subject matter and has been improperly incorporated by

reference (Weisgraber (1994), *Adv. Protein Chem.*) [see p. 3, ¶ 0009 of the specification].

MPEP §608.01(p) discusses incorporation by reference, and states, in part, that,

> *An application for a patent when filed may incorporate "essential material" by reference to (1) a U.S. patent, (2) a U.S. patent application publication, or (3) a pending U.S. application, subject to the conditions set forth below. "Essential material" is defined as that which is necessary to (1) describe the claimed invention, (2) provide an enabling disclosure of the claimed invention, or (3) describe the best mode (35 U.S.C. 112). In any application which is to issue as a U.S. patent, essential material may not be incorporated by reference to (1) patents or applications published by foreign countries or a regional patent office, (2) non-patent publications, (3) a U.S. patent or application which itself incorporates "essential material" by reference, or (4) a foreign application.*

Thus, the incorporation of essential material in the specification by reference to Weisgraber is improper because it does not particularly disclose the subject matter to be incorporated [the human apoE4 sequence and the alignment thereof]. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

Furthermore, the instant specification fails to enable the methods of utilizing the claimed transgenic mouse in methods of identifying agents that reduce a phenomenon associated with Alzheimer's disease (AD) [see claim 14-15]. The specification teaches that transgenic mice of the instant invention have a phenotype wherein the modified apoE polypeptide exhibits preferential binding to lower density lipoproteins when compared to a wild-type mouse. However, the specification fails to provide a correlation between the phenotype of the claimed transgenic mice and AD. For example, Baum *et al.* [**Microscopy Res. & Tech.**, cited on Applicants' IDS, filed 3/5/02] states that the apoE4 allele increases the risk of Alzheimer's, perhaps by acceleration of plaque formation or by neuron repair, but that the mechanism is unclear. See *Abstract* and p. 279, 1st column. Baum teach that in humans, patients with AD with apoE4 have increased amyloid deposition [see p. 278, 2nd column, 1st ¶]. Further, Dong and Weisgraber [JBC, 271:19053-19057 (1996) cited in Applicants' IDS filed 3/5/02] state that apoE plays an important role in metabolism with its interaction with the LDL receptor [see p. 19053, 2nd column, 1st ¶] and further states that the underlying mechanism(s) as to why apoE4 is a major risk factor to AD is unknown. See p. 19056, 1st column, 2nd ¶. Thus, although the state of the art provides evidence that apoE, and particularly, apoE4, is associated with AD, neither the specification nor art at the time of filing provide a nexus between the phenotype of the claimed mice [*i.e.*, that the modification of the endogenous mouse apoE4 causes the resulting polypeptide to

exhibit preferential binding to LDLs] and a phenomenon associated with AD. For example, the specification fails to show that the claimed mice have more amyloid deposition or other phenotypes associated with AD. Accordingly, the instant specification fails to enable the instant invention because it fails to show how to use the claimed mice in methods of identifying agents that reduce a phenomenon associated with AD, because the phenotype of the claimed mice is not correlated with a phenomenon associated with AD.

Accordingly, in view of the quantity of experimentation necessary for the production and use of mice comprising a modified apoE allele, wherein the modified allele encodes a modified apoE polypeptide that exhibits domain interaction characteristic of human apoE4 and the modified polypeptide comprises a Thr→Arg substitution at a position equivalent to amino acid 61 of the human apoE4, the lack of teaching or guidance provided by the specification with regard to the human apoE4 sequence, the lack of teachings, guidance or a nexus between the observed phenotype of the claimed mice and AD, it would have required undue experimentation for one of skill in the art to make and/or use the claimed non-human animals and methods of using the same.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3, 5, 7, 14, 15, 20-22 are unclear. The claims recite (or depend from claims that recite) that the modified endogenous apoE polypeptide comprises a Thr → Arg substitution *at a position equivalent to amino acid 61 of human apoE4.* This is unclear because amino acid 61 in the human apoE4 sequence is relative to the numbering of the sequence. Furthermore, it is unclear what a position "equivalent" to the amino acid 61 would be. Amendment/clarification is requested.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 3, and 5 are rejected under 35 U.S.C. 102(a) as being anticipated by Raffai *et al.* [**Circulation**, 102(18), Supplement: 11.150, Abstract (October 31, 2000].

Raffai teach the site-directed mutagenesis of mouse apoE to introduce an Arg-61 mutation, then utilized gene targeting in ES cells to create mice (+/- and -/-) with an Arg-61 mutation. It was found that in plasma from +/- mice the Arg-61 apoE preferentially bound to VLDL. Further, primary hepatocytes from the mice were isolated and found to express the Arg-61 apoE.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 14, 15, 20-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Raffai *et al.* [**Circulation**, 102(18), Supplement: 11.150, Abstract (October 31, 2000) when taken with Mucke *et al.* [**U.S. Pat. No.** 6,046,381, published April 4, 2000].

Raffai teach the site-directed mutagenesis of mouse apoE to introduce an Arg-61 mutation, then utilized gene targeting in ES cells to create mice (+/- and -/-) with an Arg-61 mutation. It was found that in plasma from +/- mice the Arg-61

apoE preferentially bound to VLDL. Further, primary hepatocytes from the mice were isolated and found to express the Arg-61 apoE. Raffai do not teach cells isolated from these transgenic mice and methods of identifying an agent that reduces a phenomenon associated with AD utilizing the transgenic mice.

However, prior to the time of the claimed invention, Mucke teach the generation of ApoE transgenic mice and methods of utilizing these mice to identify agents that reduce the symptoms of apoE-related pathologies. See col. 3-4, bridging ¶. Mucke teach that apoE related pathologies is associated with two characteristics associated with AD, amyloid deposits and neurofibrillary tangles. See col. 2, lines 19-24. Mucke further teach cells isolated from the transgenic animals, particularly cells of from neural and brain tissues. See col. 11, lines 16-26. Mucke teach the analysis of immunolabeled brain sections from the transgenic ApoE4 mice which showed the presence of astrocytes and neurons expressing the apoE4 transgene construct. See col. 22, lines 1-10.

Accordingly, in view of the combined teachings of Raffai and Mucke, it would have been obvious for one of ordinary skill in the art to use the transgenic mice comprising an Arg-61 mutation in methods of identifying agents that reduce a phenomenon associated with AD and to isolate cells from such mice. One of skill in the art would have been sufficiently motivated to use these mice in these methods to find agents to reduce symptoms of apoE-related pathologies, such as AD and one would be motivated to isolate cells from the Arg-61 transgenic mice for methods of

identifying compounds that modulate, enhance or repress apoE activity. Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Amy Nelson, Acting SPE of Art Unit 1632, at (571) 272-0804. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

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